PCT/EP04/051651

Kongeriget Danmark

Patent application No.: PA 2003 01117

Date of filing: 31 July 2003

Applicant:
(Name and address)

NeuroSearch A/S
Pederstrupvej 93
DK-2750 Ballerup
Denmark

Titlel: Novel tartrate salts

IPC:

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

24 May 2004

Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

Modtaget
31 JULI 2003

2-METHOXYMETHYL-3-(3,4-DICHLOROPHENYL)-8-AZABICYCLO[3.2.1]OCTANE TARTRATE SALTS

TECHNICAL FIELD

This invention relates to novel (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate salts, such as L-tartrate monohydrates and anhydrates. The salts are useful as monoamine neurotransmitter re-uptake inhibitors.

In other aspects the invention relates to the use of these salts in a method for therapy and to pharmaceutical compositions comprising the salts of the invention.

BACKGROUND ART

The compound (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane is disclosed in WO 97/30997 (NeuroSearch A/S). Therein, the citrate salt was prepared (Example 15).

For commercial use, however, it is important to have a physiologically acceptable salt with an optimal combination of stability, solubility, non-hygroscopicity, bioavailablity and good handling properties, such as a well defined melting point and a reproducible crystalline form.

SUMMARY OF THE INVENTION

In its first aspect, the invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a salt of the invention, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a salt of the invention, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to inhibition of monoamine neurotransmitter re-uptake in the central

nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a salt of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate

In its first aspect the present invention provides a salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

In one embodiment, the salt is selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a second embodiment, the salt is (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

In a further embodiment, the salt is an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

In a still further embodiment, the salt is the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

In a further embodiment, the salt is the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

Any combination of two or more of the embodiments as described above is considered within the scope of the present invention.

Hydrated forms

The salt of the invention may be provided in anhydrous forms or hydrated forms. Hydrated forms include the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like.

Labelled Compounds

The salts of the invention may be used in their labelled or unlabelled form. In the context of this invention "label" stands for the binding of a marker to the salt of interest that will allow easy quantitative detection of said salt.

The labelled salts of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled salt of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^{2}H (deuterium), ^{3}H (tritium), ^{13}C, and ^{14}C.

Methods of Preparation

The salts of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one salt of the invention can be converted to another salt of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

Salts of the invention may be tested for their ability to inhibit reuptake of the monoamines dopamine, noradrenaline and serotonin in synaptosomes eg such as described in WO 97/30997. Based on the balanced activity observed in these tests the salts of the invention is considered useful for the treatment the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

In a special embodiment, the salts of the invention are considered useful for the treatment, prevention or alleviation of: mood disorder, depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder (OCD), panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder (ADHD), obesity, anxiety, eating disorder, Parkinson's disease, parkinsonism, Alzheimers disease, dementia, presenile dementia, dementia of ageing, senile dementia, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, drug addiction, post-traumatic stress disorder, acute stress disorder, anxiety, generalized anxiety disorder, drug misuse, cocaine abuse, tobacco abuse, alcoholism, pain, migraine pain, tension-type headache, fibromyalgia, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, or Gilles de la Tourettes disease.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 100 mg API per day, more preferred of from about 0.1 to about 10 mg API per day, most preferred of from about 0.5 to about 5 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the salt of the invention.

While a salt of the invention for use in therapy may be administered in the form of the raw salt, it is preferred to introduce the active ingredient, in a pharmaceutical

composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the salt of the invention, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 10 mg of active ingredient per individual dose, preferably of from about 0.5 to about 5 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, and which

method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a salt of the invention.

Suitable dosage ranges are dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane citrate salt

The citrate salt of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane was synthesized as described in WO 97/30997 (Example 15).

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane

The free base was obtained from dissolving the citrate salt in water and adjusting pH to 10-13 with aqueous base, followed with extraction with toluene. The toluene phase was collected, dried end evaporated to dryness. This left the free base as an oil.

Example 2

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I)

To a heated solution of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane (the free base) in aqueous ethanol was added L-tartaric acid. The warm mixture was treated with activated charcoal and filtered. The filtrate was cooled and (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo-[3.2.1]octane was isolated as the L-tartrate monohydrate.

Form I is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	12.05	14.21	16.37	17.4	18.34	19.29	19.58	20.27	23.3	23.75
d space (Å)	7.3	6.2	5.4	5.1	4.8	4.6	4.5	4.4	3.8	3.7
Peak	11	12	13	14	15	16	17			
2 Theta ° (Cu Kα)	24.37	26.11	26.76	28.25	28.72	29.25	29.82			
d space (Å)	3.6	3.4	3.3	3.2	3.1	3.1	3.0			

Example 3

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form II)

The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated in a TGA AlO_2 crucible to 125°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

Form II is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

Example 4

(1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate (Form III)

The form was prepared thermal dehydration. (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate (Form I) was heated in a TGA AlO_2 crucible to 160°C, 10°C/min. The salt was allowed to cool before opening the TGA furnace. During heating and cooling the furnace was purged with 50ml/min dry nitrogen.

Form III is characterized by the following principal peaks in its X-ray powder diffraction pattern shown below:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

CLAIMS

1. A salt selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane tartrate.

2. The salt of claim 1 being selected from the anhydrous and hydrated forms of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

3. The salt of claim 1, being (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate monohydrate.

4. The salt of claim 1, being an anhydrous form of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate.

5. The salt of claim 4, being the polymorphic form (form II) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	10.35	11.68	12.53	14.81	15	15.77	16.82	17.41	17.77	18.87
d space (Å)	8.5	7.6	7.1	6.0	5.9	5.6	5.3	5.1	5.0	4.7
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	20.29	21.26	21.66	23.44	23.73	25.44	25.99	27.58	28.14	
d space (Å)	4.4	4.2	4.1	3.8	3.7	3.5	3.4	3.2	3.2	

6. The salt of claim 4, being the polymorphic form (form III) of (1R,2R,3S,5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane L-tartrate anhydrate characterized by the following principal peaks in its X-ray powder diffraction pattern:

Peak No.	1	2	3	4	5	6	7	8	9	10
2 Theta ° (Cu Kα)	5.37	10.6	10.82	11.58	11.88	12.79	14.78	16.27	16.5	17.03
d space (Å)	16.4	8.3	8.2	7.6	7.4	6.9	6.0	5.4	5.4	5.2
Peak	11	12	13	14	15	16	17	18	19	
2 Theta ° (Cu Kα)	17.84	19.29	20.01	21.2	22.99	23.46	24.54	25.15	26.59	
d space (Å)	5.0	4.6	4.4	4.2	3.9	3.8	3.6	3.5	3.3	

7. A pharmaceutical composition, comprising a therapeutically effective amount of a salt of any one of claims 1-6, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

8. Use of a salt of any of claims 1-6 for the manufacture of a medicament.

9. The use according to claim 8, for the manufacture of a pharmaceutical pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system.

10. The use according to claim 9, wherein the disease, disorder or condition is mood disorder, depression, major depressive disorder, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, mood disorder due to a general medical condition, substance-induced mood disorder, pseudodementia, Ganser's syndrome, obsessive compulsive disorder (OCD), panic disorder, panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, panic attack, memory deficits, memory loss, attention deficit hyperactivity disorder (ADHD), obesity, anxiety, eating disorder, Parkinson's disease, parkinsonism, Alzheimers disease, dementia, presenile dementia, dementia of ageing, senile dementia, acquired immunodeficiency syndrome dementia complex, memory dysfunction in ageing, specific phobia, social phobia, drug addiction, post-traumatic stress disorder, acute stress disorder, anxiety, generalized anxiety disorder, drug misuse, cocaine abuse, tobacco abuse, alcoholism, pain, migraine pain, tension-type headache, fibromyalgia, bulimia, premenstrual syndrome, late luteal phase syndrome, post-traumatic syndrome, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, sleep disorders, autism, mutism, trichotillomania, narcolepsy, or Gilles de la Tourettes disease.

11. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to inhibition of monoamine neurotransmitter re-uptake in the central nervous system, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a salt according to any one of the claims 1-6.